INVENTOR SEARCH

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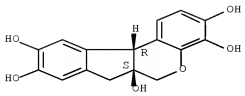
L8 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:316356 HCAPLUS Full-text
DOCUMENT NUMBER: 142:367666
TITLE: Compositions and methods using farnesoid X receptor agonists for treatment of fibrosis
INVENTOR(S): Liu, Yaping; Moore, John Tomlin
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA; Jones, Stacey Ann
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005032549	A1	20050414	WO 2004-US29748	20040910
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1696910	A1	20060906	EP 2004-783821	20040910
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR				
US 20070015796	A1	20070118	US 2006-572974	20060322
PRIORITY APPLN. INFO.:			US 2003-506394P	P 20030926
			WO 2004-US29748	W 20040910

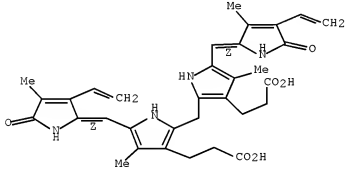
OTHER SOURCE(S): MARPAT 142:367666
AB Methods for the treatment of fibrosis, including liver fibrosis, via administration of FXR agonists are provided. FXR agonist GW4064 reduced collagen deposition in livers of rats treated with CCl4.
IT 517-28-2 635-65-4 9000-86-6
9000-97-9 9001-60-9 9001-78-9
9002-02-2 9003-98-9 9046-27-9
17372-87-1 65666-07-1 192526-67-3
RL: PRPH (Prophetic)
(Compositions and methods using farnesoid X receptor agonists for treatment of fibrosis)
RN 517-28-2 HCAPLUS
CN Benz[b]indeno[1,2-d]pyran-3,4,6a,9,10(6H)-pentol, 7,11b-dihydro-, (6aS,11bR)- (CA INDEX NAME)

Absolute stereochemistry.



RN 635-65-4 HCAPLUS
CN 21H-Biline-8,12-dipropanoic acid, 2,17-diethenyl-1,10,19,22,23,24-hexahydro-3,7,13,18-tetramethyl-1,19-dioxo- (CA INDEX NAME)

Double bond geometry as shown.



RN 9000-86-6 HCAPLUS
CN Aminotransferase, alanine (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9000-97-9 HCAPLUS
CN Aminotransferase, aspartate (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9001-60-9 HCAPLUS
CN Dehydrogenase, lactate (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9001-78-9 HCAPLUS
CN Phosphatase, alkaline (CA INDEX NAME)

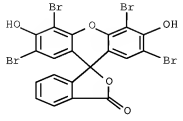
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9002-02-2 HCAPLUS
CN Dehydrogenase, succinate (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9003-98-9 HCAPLUS
CN Nuclease, deoxyribo- (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9046-27-9 HCAPLUS
CN Glutamyltransferase, γ- (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 17372-87-1 HCAPLUS
CN Spiro[isobenzofuran-1(3H),9'-[9H]xanthen]-3-one,

2',4',5',7'-tetrabromo-3',6'-dihydroxy-, sodium salt (1:2) (CA INDEX NAME)



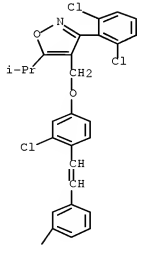
●2 Na

RN 65666-07-1 HCAPLUS
CN Silymarin (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 192526-67-3 HCAPLUS
CN TRIzol (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as farnesoid X receptor agonist; farnesoid X receptor agonists for treatment of fibrosis)
RN 278779-30-9 HCAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (CA INDEX NAME)

PAGE 1-A



HO2C

IT 140208-24-8, TIMP1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(farnesoid X receptor agonists for treatment of fibrosis)
RN 140208-24-8 HCAPLUS
CN Proteinase inhibitor, TIMP 1 (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT 849654-17-7 849654-18-8 849654-19-9
849654-20-2 849654-21-3 849654-22-4
849654-23-5 849654-24-6 849654-25-7
849654-26-8 849654-27-9 849654-28-0
849654-29-1 849654-30-4 849654-31-5
RL: PRP (Properties)
(unclaimed nucleotide sequence; compns. and methods using farnesoid X receptor agonists for treatment of fibrosis)
RN 849654-17-7 HCAPLUS
CN DNA, d(T-C-C-T-G-A-C-C-C-T-G-A-A-G-T-A-T-C-C-G-A-T-A) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 849654-18-8 HCAPLUS
CN DNA, d(G-G-T-G-C-C-A-G-A-T-C-T-T-T-T-C-C-A-T-G-T-C) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 849654-19-9 HCAPLUS
CN DNA, d(A-A-C-A-C-G-G-C-A-T-C-A-T-C-A-C-C-A-A-C-T-G-G-G-A) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 849654-20-2 HCAPLUS
CN DNA, d(T-T-C-A-C-C-T-A-C-A-G-C-A-C-G-C-T-T-G-T-G) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 849654-21-3 HCAPLUS
CN DNA, d(G-A-T-G-A-C-T-G-T-C-T-T-G-C-C-C-C-A-A-G-T-T) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 849654-22-4 HCAPLUS
CN DNA, d(A-T-G-G-C-T-G-C-A-C-G-A-G-T-C-A-C-A-C-C-G) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 849654-23-5 HCAPLUS
CN DNA, d(C-C-A-A-A-G-C-C-A-C-C-G-G-A-G-T-C-T-T) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 849654-24-6 HCAPLUS
CN DNA, d(G-C-T-T-G-A-A-G-C-C-A-A-T-C-C-T-T-G-G-A) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 849654-25-7 HCAPLUS
CN DNA, d(C-T-C-T-G-C-G-C-T-C-C-A-T-T-C-C-A-C-C-T-T-A-T-A-A-C-A-C-C) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 849654-26-8 HCAPLUS
CN DNA, d(G-A-A-C-C-G-C-A-G-C-G-A-G-G-A-G-T-T-T) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 849654-27-9 HCAPLUS
CN DNA, d(G-G-C-A-G-T-G-A-T-G-T-G-C-A-A-A-T-T-T-C-C) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 849654-28-0 HCAPLUS
CN DNA, d(T-C-A-T-C-G-C-G-G-G-C-C-G-T-T-T-A-A-G-G-A-A) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 849654-29-1 HCAPLUS
CN DNA, d(G-C-T-G-C-T-G-A-C-C-C-C-C-A-C-T-G-A-T) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 849654-30-4 HCAPLUS
CN DNA, d(G-C-C-A-C-T-G-C-C-G-G-A-C-A-A-C-T-C) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 849654-31-5 HCAPLUS
CN DNA, d(C-G-C-C-T-G-A-G-T-G-G-C-T-G-T-C-T-T-T-T-G-A-C-G-T) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

RESULTS FROM REGISTRY AND CAPLUS

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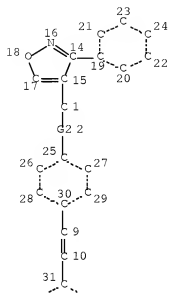
L9 STR



Page 1-A

Page 2-A
VAR G1=CH/N
VAR G2=O/NH
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 27

STEREO ATTRIBUTES: NONE
L11 45 SEA FILE=REGISTRY SSS FUL L9
L14 10 SEA FILE=HCAPLUS ABB=ON L11 AND (?LIVER? OR ?HEPAT?)(W)(?DISEA
S? OR ?FIBROSIS?)

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L14 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:383580 HCAPLUS Full-text
DOCUMENT NUMBER: 144:404429
TITLE: A method using farnesoid X receptor (FXR) agonists

with PPAR agonists for reducing drug-induced adverse side effects in a patient
INVENTOR(S): Fiorucci, Stefano; Pellicciari, Roberto; Pruzanski, Mark
PATENT ASSIGNEE(S): Intercept Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006044391	A1	20060427	WO 2005-US36536	20051014
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20060252670	A1	20061109	US 2005-250298	20051013
AU 2005295888	A1	20060427	AU 2005-295888	20051014
CA 2584284	A1	20060427	CA 2005-2584284	20051014
EP 1814582	A1	20070808	EP 2005-807696	20051014
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
JP 2008516955	T	20080522	JP 2007-536810	20051014
PRIORITY APPLN. INFO.:			US 2004-619381P	P 20041014
			WO 2005-US36536	W 20051014

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

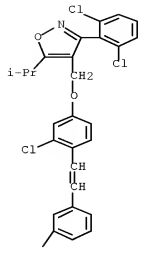
AB The invention relates to the discovery that farnesoid X receptor (FXR) agonists can be used in combination with peroxisome proliferation activated receptor γ (PPARγ) agonists to reduce drug-induced adverse side effects in patients suffering from conditions such as insulin resistance, Type II diabetes, metabolic syndrome, non-alc. fatty liver disease (NAFLD), non-alc. steatohepatitis (NASH), and heart disease. Particularly, the invention encompasses methods for treating patients suffering from drug-induced adverse side effects with selective PPARγ, dual PPARα/γ and pan PPARα/γ/δ agonists in combination with FXR agonists.

IT 278779-30-9, GW4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(FXR agonist combination with PPAR agonist for reduction of drug-induced adverse effects)

RN 278779-30-9 HCAPLUS

CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:1077095 HCAPLUS Full-text
DOCUMENT NUMBER: 143:339369
TITLE: Cross-talk between farnesoid-X-receptor (FXR) and peroxisome proliferator-activated receptor γ contributes to the antifibrotic activity of FXR ligands in rodent models of liver cirrhosis
AUTHOR(S): Fiorucci, Stefano; Rizzo, Giovanni; Antonelli, Elisabetta; Renga, Barbara; Mencarelli, Andrea; Riccardi, Luisa; Morelli, Antonio; Pruzanski, Mark; Pellicciari, Roberto
CORPORATE SOURCE: Dipartimento di Medicina Clinica e Sperimentale, Universita degli Studi di Perugia, Perugia, Italy
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2005), 315(1), 58-68
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The nuclear receptors farnesoid X receptor (FXR) and peroxisome proliferator-activated receptor (PPAR)γ exert counterregulatory effects on hepatic stellate cells (HSCs) and protect against liver fibrosis development in rodents. Here, we investigated whether FXR ligands regulate PPARγ expression in HSCs and models of liver fibrosis induced in rats by porcine serum and carbon

tetrachloride administration and bile duct ligation. Our results demonstrate that HSCs trans-differentiation associated with suppression of PPARγ mRNA expression, whereas FXR mRNA was unchanged. Exposure of cells to natural and synthetic ligands of FXR, including 6-Et chenodeoxycholic acid (6-ECDCA), a synthetic derivative of chenodeoxycholic acid, reversed this effect and increased PPARγ mRNA by ≈40-fold. Submaximally effective concns. of FXR and PPARγ ligands were additive in inhibiting α1(I) collagen mRNA accumulation induced by transforming growth factor (TGF)β1. Administration of 6-ECDCA in rats rendered cirrhotic by porcine serum and carbon tetrachloride administration or bile duct ligation reverted down-regulation of PPARγ mRNA expression in HSCs. Cotreatment with 6-ECDCA potentiates the antifibrotic activity of rosiglitazone, a PPARγ ligand, in the porcine serum model as measured by morphometric anal. of liver collagen content, hydroxyproline, and liver expression of α1(I) collagen mRNA, α-smooth muscle actin, fibronectin, TGFβ1, and tissue inhibitor of metalloprotease 1 and 2, whereas it enhanced the expression of PPARγ and uncoupling protein 2, a PPARγ-regulated gene, by 2-fold. In conclusion, by using an in vitro and in vivo and in vivo approach, we demonstrated that FXR ligands up-regulate PPARγ mRNA in HSCs and in rodent models of liver fibrosis. A FXR-PPARγ cascade exerts counter-regulatory effects in HSCs activation.

IT 278779-30-9, GW 4064

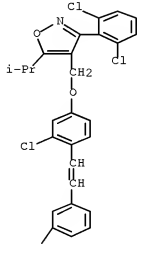
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antifibrotic activity of FXR ligands mediated by cross-talk between FXR and PPARγ in rodent liver cirrhosis model)

RN 278779-30-9 HCAPLUS

CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

HO2C

OS.CITING REF COUNT: 32 THERE ARE 32 CAPLUS RECORDS THAT CITE THIS RECORD (32 CITINGS)
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:1049799 HCAPLUS Full-text
DOCUMENT NUMBER: 143:319188
TITLE: Treatment of fibrosis using farnesoid X receptor (FXR) ligands
INVENTOR(S): Fiorucci, Stefano; Pellicciari, Roberto; Pruzanski, Mark
PATENT ASSIGNEE(S): Intercept Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005089316	A2	20050929	WO 2005-US8575	20050314
WO 2005089316	A3	20060406		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005222994	A1	20050929	AU 2005-222994	20050314
CA 2559476	A1	20050929	CA 2005-2559476	20050314
US 20060069070	A1	20060330	US 2005-81002	20050314
EP 1734970	A2	20061227	EP 2005-729394	20050314
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
JP 2007529427	T	20071025	JP 2007-503111	20050314
PRIORITY APPLN. INFO.:			US 2004-552865P P	20040312
			WO 2005-US8575 W	20050314

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

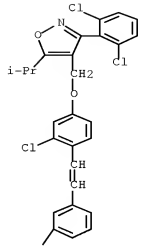
AB The invention discloses a method for inhibiting fibrosis that occurs in an organ where the farnesoid X receptor (FXR) is expressed. The method involves administering a high potency, activating ligand of FXR in an effective amount to a patient who is not suffering from a cholestatic condition. The invention also provides pharmaceutical compns. containing an effective amount of an FXR ligand and kits for dispensing the pharmaceutical compns.

IT 278779-30-9, GW4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(farnesoid X receptor ligands for treatment of fibrosis)

RN 278779-30-9 HCAPLUS

CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:413517 HCAPLUS Full-text
DOCUMENT NUMBER: 142:441633
TITLE: Protective effects of 6-ethyl chenodeoxycholic acid, a farnesoid X receptor ligand, in estrogen-induced cholestasis
AUTHOR(S): Fiorucci, Stefano; Clerici, Carlo; Antonelli, Elisabetta; Orlandi, Stefano; Goodwin, Bryan; Sadeghpour, Bahman M.; Sabatino, Giuseppe; Russo, Giuseppe; Castellani, Danilo; Willson, Timothy M.; Pruzanski, Mark; Pellicciari, Roberto; Morelli, Antonio
CORPORATE SOURCE: Clinica di Gastroenterologia ed Epatologia, Dipartimento di Medicina Clinica e Sperimentale Universita degli Studi di Perugia, Perugia, Italy
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2005), 313(2), 604-612
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The farnesoid X receptor (FXR), an endogenous sensor for bile acids, regulates a program of genes involved in bile acid biosynthesis, conjugation, and transport. Cholestatic liver diseases are a group of immunol. and genetically mediated disorders in which accumulation of endogenous bile acids plays a role in the disease progression and symptoms. Here, the authors describe the

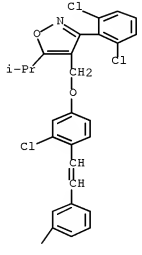
effect of 6-Et chenodeoxycholic acid (6-ECDCA or INT-747), a semisynthetic bile acid derivative and potent FXR ligand, in a model of cholestasis induced by 5-day administration of 17α-ethynylestradiol (E2 17α) to rats. The exposure of rat hepatocytes to 1 μM 6-ECDCA caused a 3- to 5-fold induction of small heterodimer partner (Shp) and bile salt export pump (bsep) mRNA and 70 to 80% reduction of cholesterol 7α-hydroxylase (cyp7a1), oxysterol 12β-hydroxylase (cyp8b1), and Na+/taurocholate cotransporting peptide (ntcp). In vivo administration of 6-ECDCA protects against cholestasis induced by E2 17α. Thus, 6-ECDCA reverted bile flow impairment induced by E2 17α, reduced secretion of cholic acid and deoxycholic acid, but increased muricholic acid and chenodeoxycholic acid secretion. In vivo administration of 6-ECDCA increased liver expression of Shp, bsep, multidrug resistance-associated protein-2, and multidrug resistance protein-2, whereas it reduced cyp7a1 and cyp8b1 and ntcp mRNA. These changes were reproduced by GW4064, a synthetic FXR ligand. In conclusion, by demonstrating that 6-ECDCA protects against E2 17α cholestasis, the authors' data support the notion that development of potent FXR ligands might represent a new approach for the treatment of cholestatic disorders.

IT 278779-30-9, GW4064
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); BIOL (Biological study)
(chenodeoxycholic acid derivative protection against estrogen-induced cholestasis and mechanisms thereof)

RN 278779-30-9 HCAPLUS

CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

OS.CITING REF COUNT: 45 THERE ARE 45 CAPLUS RECORDS THAT CITE THIS RECORD (45 CITINGS)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:316356 HCAPLUS Full-text
DOCUMENT NUMBER: 142:367666
TITLE: Compositions and methods using farnesoid X receptor agonists for treatment of fibrosis
INVENTOR(S): Liu, Yaping; Moore, John Tomlin
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA; Jones, Stacey Ann
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005032549	A1	20050414	WO 2004-US29748	20040910
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1696910	A1	20060906	EP 2004-783821	20040910
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR				
US 20070015796	A1	20070118	US 2006-572974	20060322
PRIORITY APPLN. INFO.:			US 2003-506394P	P 20030926
			WO 2004-US29748	W 20040910

OTHER SOURCE(S): MARPAT 142:367666

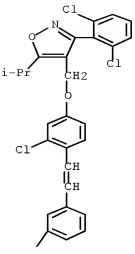
AB Methods for the treatment of fibrosis, including liver fibrosis, via administration of FXR agonists are provided. FXR agonist GW4064 reduced collagen deposition in livers of rats treated with CCl4.

IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as farnesoid X receptor agonist; farnesoid X receptor agonists for treatment of fibrosis)

RN 278779-30-9 HCAPLUS

CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:1061036 HCAPLUS Full-text
DOCUMENT NUMBER: 142:232933
TITLE: The nuclear receptor SHP mediates inhibition of hepatic stellate cells by FXR and protects against liver fibrosis
AUTHOR(S): Fiorucci, Stefano; Antonelli, Elisabetta; Rizzo, Giovanni; Renga, Barbara; Mencarelli, Andrea; Riccardi, Luisa; Orlandi, Stefano; Pellicciari, Roberto; Morelli, Antonio
CORPORATE SOURCE: Dipartimento di Medicina Clinica e Sperimentale, Clinica di Gastroenterologia ed Endoscopia Digestiva, Perugia, Italy
SOURCE: Gastroenterology (2004), 127(5), 1497-1512
CODEN: GASTAB; ISSN: 0016-5085
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background & Aims: The farnesoid X receptor (FXR) is an endogenous sensor for bile acids and inhibits bile acid synthesis by inducing small heterodimer partner (SHP) gene expression. The aim of this study was to investigate whether FXR is expressed by and modulates function of hepatic stellate cells (HSCs). Methods: The antifibrotic activity of FXR ligand was tested in 2 rodent models: the porcine serum and bile duct ligation (BDL). Results: Twelve-week administration of 1-10 mg/kg 6-Et chenodeoxycholic acid (6-ECDCA), a synthetic FXR ligand, to porcine serum-treated rats prevented liver fibrosis development and reduced liver expression of α1(I) collagen, TGF-β1 and α-SMA

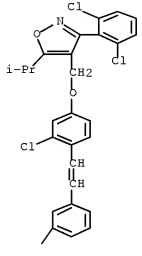
mRNA by .apprx.90%. Therapeutic administration of 6-ECDCA, 3 mg/kg, to BDL rats reduced liver fibrosis and α1(I) collagen, transforming growth factor (TGF)-β1, α-SMA, and tissue metalloproteinase inhibitor (TIMP)-1 and 2 mRNA (mRNA) by 70%-80%. No protection was observed in BDL rats treated with CDCA, 3 mg/kg, and ursodeoxycholic acid, 15 mg/kg. FXR expression was detected in HSCs. Exposure of HSCs to FXR ligands caused a 3-fold increase of SHP, reduced α1(I)collagen and TGF-β1 by .apprx.60%-70% and abrogates α1(I) collagen mRNA up-regulation induced by thrombin and TGF-β1. By retrovirus infection and small interference RNA, we generated SHP overexpressing and SHP-deficient HSC-T6. Using these cell lines, we demonstrated that SHP binds JunD and inhibits DNA binding of adaptor protein (AP)-1 induced by thrombin. Conclusions: By demonstrating that an FXR-SHP regulatory cascade promotes resolution of liver fibrosis, this study establish that FXR ligands might represent a novel therapeutic option to treat liver fibrosis.

IT 278779-30-9, GW4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(GW4064 reduced α1(I) collagen in HSCs and immortalized HSP-T6 cell line)

RN 278779-30-9 HCAPLUS

CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

OS.CITING REF COUNT: 63 THERE ARE 63 CAPLUS RECORDS THAT CITE THIS RECORD (64 CITINGS)

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2004:630391 HCAPLUS Full-text
DOCUMENT NUMBER: 142:273060
TITLE: The nuclear bile acid receptor FXR as a novel therapeutic target in cholestatic liver diseases: Hype or hope?
AUTHOR(S): Trauner, Michael
CORPORATE SOURCE: Laboratory of Experimental and Molecular Hepatology, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University Graz, Graz, Austria
SOURCE: Hepatology (Hoboken, NJ, United States) (2004), 40(1), 260-263
CODEN: HPTLD9; ISSN: 0270-9139
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

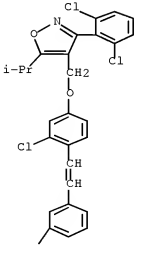
AB A review. A polemic in response to Liu et al. (J. Clin. Invest., 2003, 112, 1678-1687) is presented. Liu et al. investigated the effects of the farnesoid X receptor agonist GW4064 and tauroursodeoxycholic acid (TUDCA) as clin. comparator in α-naphthylisothiocyanate (ANIT)-treated and common bile duct ligated (CBDL) rats as models of intrahepatic and extrahepatic cholestasis, resp. Some of conceptual and methodol. limitations of the study of Liu et al. are discussed. However, despite these limitations, their study indicates an important new direction in the treatment of cholestasis. This concept needs to be refined by the use of more gene-selective agonists and combination approaches targeting both regular/orthograde (FXR-dependent) and alternative/retrograde pathways of bile acid transport and metabolism

IT 278779-30-9, GW4064
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nuclear bile acid receptor FXR as therapeutic target in cholestatic liver diseases)

RN 278779-30-9 HCAPLUS

CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (CA INDEX NAME)

PAGE 1-A



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OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

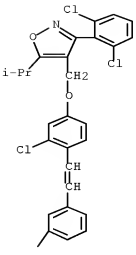
L14 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:973413 HCAPLUS Full-text
DOCUMENT NUMBER: 140:229012
TITLE: Hepatoprotection by the farnesoid X receptor agonist GW4064 in rat models of intra- and extrahepatic cholestasis
AUTHOR(S): Liu, Yaping; Binz, Jane; Numerick, Mary Jo; Dennis, Steve; Luo, Guizhen; Desai, Bhasha; MacKenzie, Kathleen I.; Mansfield, Traci A.; Kliewer, Steven A.; Goodwin, Bryan; Jones, Stacey A.
CORPORATE SOURCE: Nuclear Receptor Functional Analysis, High Throughput Biology, GlaxoSmithKline, Research Triangle Park, NC, USA
SOURCE: Journal of Clinical Investigation (2003), 112(11), 1678-1687
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Farnesoid X receptor (FXR) is a bile acid-activated transcription factor that is a member of the nuclear hormone receptor superfamily. Fxr-null mice exhibit a phenotype similar to Byler disease, an inherited cholestatic liver disorder. In the liver, activation of FXR induces transcription of transporter genes involved in promoting bile acid clearance and represses genes involved in bile acid biosynthesis. We investigated whether the synthetic FXR agonist GW4064 could protect against cholestatic liver damage in rat models of extrahepatic and intrahepatic cholestasis. In the bile duct-ligation and α-naphthylisothiocyanate models of cholestasis, GW4064 treatment resulted in significant redns. in serum alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase, as well as other markers of liver damage. Rats that received GW4064 treatment also had decreased incidence and extent of necrosis, decreased inflammatory cell infiltration, and decreased bile duct proliferation. Anal. of gene expression in livers from GW4064-treated cholestatic rats revealed decreased expression of bile acid biosynthetic genes and increased expression of genes involved in bile acid transport, including the phospholipid flippase MDR2. The hepatoprotection seen in these animal models by the synthetic FXR agonist suggests FXR agonists may be useful in the treatment of cholestatic liver disease.

IT 278779-30-9, GW4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hepatoprotection by farnesoid X receptor agonist GW4064 in rat models of intra- and extrahepatic cholestasis)

RN 278779-30-9 HCAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (CA INDEX NAME)

PAGE 1-A



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L14 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:855658 HCAPLUS Full-text
DOCUMENT NUMBER: 139:317457
TITLE: Compositions and methods using farnesoid X receptor ligands for hepatoprotection and treatment of cholestasis
INVENTOR(S): Kliewer, Steven Anthony; Willson, Timothy Mark
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 8 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20030203939	A1	20031030	US 2002-132311	20020425
US 6987121	B2	20060117		
WO 2003090745	A1	20031106	WO 2003-US10519	20030407

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2003226283 A1 20031110 AU 2003-226283 20030407

EP 1501506 A1 20050202 EP 2003-747270 20030407

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.: US 2002-132311 A 20020425

WO 2003-US10519 W 20030407

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 139:317457

AB Methods for the treatment of cholestatic liver disease and reduction and prevention of hepatic injury resulting from cholestasis via administration of a FXR ligand are provided. Bile duct-ligated rats treated with FXR ligand GW4064 had a pronounced improvement in liver function as defined by a reduction in a panel of liver disease serum marker enzymes.

IT 278779-30-9, GW4064

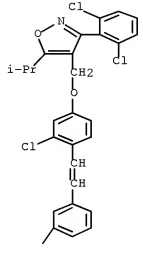
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(FXR agonist; farnesoid X receptor ligands for hepatoprotection and treatment of cholestasis)

RN 278779-30-9 HCAPLUS

CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

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REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

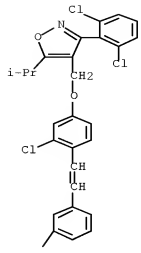
L14 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:677926 HCAPLUS Full-text
DOCUMENT NUMBER: 138:49877
TITLE: Lithocholic acid decreases expression of bile salt export pump through farnesoid X receptor antagonist activity
AUTHOR(S): Yu, Jinghua; Lo, Jane-L.; Huang, Li; Zhao, Annie; Metzger, Edward; Adams, Alan; Meinke, Peter T.; Wright, Samuel D.; Cui, Jisong
CORPORATE SOURCE: Department of Atherosclerosis and Endocrinology, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Journal of Biological Chemistry (2002), 277(35), 31441-31447
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bile salt export pump (BSEP) is a major bile acid transporter in the liver. Mutations in BSEP result in progressive intrahepatic cholestasis, a severe liver disease that impairs bile flow and causes irreversible liver damage. BSEP is a target for inhibition and down-regulation by drugs and abnormal bile salt metabolites, and such inhibition and down-regulation may result in bile acid retention and intrahepatic cholestasis. In this study, we quant. analyzed the regulation of BSEP expression by FXR ligands in primary human hepatocytes and HepG2 cells. We demonstrate that BSEP expression is dramatically regulated by ligands of the nuclear receptor farnesoid X receptor (FXR). Both the endogenous FXR agonist chenodeoxycholate (CDCA) and synthetic FXR ligand GW4064 effectively increased BSEP mRNA in both cell types. This up-regulation was readily detectable at as early as 3 h, and the ligand potency for BSEP regulation correlates with the intrinsic activity on FXR. These results suggest BSEP as a direct target of FXR and support the recent report that the BSEP promoter is transactivated by FXR. In contrast to CDCA and GW4064, lithocholate (LCA), a hydrophobic bile acid and a potent inducer of cholestasis, strongly decreased BSEP expression. Previous studies did not identify LCA as an FXR antagonist ligand in cells, but we show here that LCA is an FXR antagonist with partial agonist activity in cells. In an in vitro coactivator association assay, LCA decreased CDCA- and GW4064-induced FXR activation with an IC50 of 1 μM. In HepG2 cells, LCA also effectively antagonized GW4064-enhanced FXR transactivation. These data suggest that the toxic and cholestat effect of LCA in animals may result from its down-regulation of BSEP through FXR. Taken together, these observations indicate that FXR plays an important role in BSEP gene expression and that FXR ligands may be potential therapeutic drugs for intrahepatic cholestasis.

IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(endogenous FXR agonist chenodeoxycholate and synthetic FXR ligand GW4064 effectively increases BSEP (bile salt export pump) mRNA in primary human hepatocytes and HepG2 cells)

RN 278779-30-9 HCAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (CA INDEX NAME)

PAGE 1-A



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SEARCH HISTORY

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L2          131 SEA ABB=ON  "LIU YAPING"/AU
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                SELECT RN L6 1

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L14          10 SEA ABB=ON  L11 AND (?LIVER? OR ?HEPAT?)(W)(?DISEAS? OR
                ?FIBROSIS?)

     FILE HOME

     FILE HCAPLUS

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FILE LAST UPDATED: 2 Dec 2009 (20091202/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2009

HCAplus now includes complete International Patent Classification (IPC) reclassification data for the third quarter of 2009.

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This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE REGISTRY
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Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html